

File Copy

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 9/12	A1	(11) International Publication Number: WO 97/40819 (43) International Publication Date: 6 November 1997 (06.11.97)
(21) International Application Number: PCT/US97/06621 (22) International Filing Date: 21 April 1997 (21.04.97) (30) Priority Data: 60/016,428 29 April 1996 (29.04.96) US (71) Applicant: DURA PHARMACEUTICALS, INC. [US/US]; 5880 Pacific Center Boulevard, San Diego, CA 92121 (US). (72) Inventors: SCHULTZ, Robert; 5880 Pacific Center Boulevard, San Diego, CA 92121 (US); WITHAM, Clyde; 5880 Pacific Center Boulevard, San Diego, CA 92121 (US); HILL, Malcolm; 5880 Pacific Center Boulevard, San Diego, CA 92121 (US). (74) Agents: OHRINER, Kenneth, H. et al.; Lyon & Lyon, L.L.P., Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071- 2066 (US).		(81) Designated States: AU, BG, BR, CA, CN, CZ, FI, HU, IL, JP, KP, KR, MN, MX, NO, NZ, PL, RO, SG, SK, TR, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: METHODS OF DRY POWDER INHALATION (57) Abstract A method for inhalation of a dry powder drug includes the steps of providing a dry powder drug composition having a drug particle size of from about 1-7 microns and a mass median aerodynamic diameter of the delivered aerosol of from about 3.5 to 5.5 microns. This composition is loaded into an inhaler which is generally flow rate independent, and with the inhaler having an inspiration flow resistance of about .12 to .21 (cmH ₂ O) ^{1/2} over the range of about 15-60 L/min. The patient inhales the drug composition from the inhaler with an inspiration flow rate of about 15-60 L/min, resulting in a delivery efficiency measured by respirable fraction greater than 20 %.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DESCRIPTIONMethods of Dry Powder InhalationState-of-the-Art

5 Considerable information regarding the in-vitro and
in viv-performance of metered dose inhalers and dry powder
inhalers has been reported in literature. In general,
metered dose inhalers are inhalation flow rate
independent, but require significant coordination and even
10 then will deliver only about 20% of the nominal does to
the lungs. Radiolabelled deposition studies of metered
dose inhalers typically demonstrate the usual 3 micron
particles deposit mainly in the more central airways.
Recently, 3M Corporation, Minneapolis, MN, USA, has
presented data that indicates that if the particle size
15 could be reduced to a mass median aerodynamic diameter
(MMAD) of 1.5 microns an increase in the total amount of
particles and peripheral deposition could result. This
result appears to confirm the more uniform belief that
smaller particles are required to maximize peripheral
20 deposition (i.e. particles in the 1-2 microns size range).

Now in the case of dry powder inhalers, most studies
have shown the major issue surrounding dry powder delivery
is related to the flow rate dependence. The performance
of the dry powder inhalers now in use vary significantly
25 with inhalation flow rates ranging from 15 to 120
liters/min inspiratory effort. In general, at least 60
liters/min inspiratory flow has been required to
consistently deaggregate a dry powder sufficiently to
result in particles which could be inhaled. For some

products, inhalation flow rates significantly greater than 60 L/min are required before sufficient deaggregation can occur. Both the total amount of drug formulation delivered to the patient as well as the aerodynamic particle size are affected by increasing the inhalation flow rate. For example, at 30 L/min, aerodynamic sizes of the active particles may be as large as 8 to 10 microns but above 60 L/min the same metered dose inhaler formulation may be 2-4 microns. In addition, the dose-to-dose variation may be significantly greater as the flow rate is decreased.

Unfortunately, requiring the patient to breathe forcefully when using a metered dose inhaler is in direct opposition to maximizing deposition. Traditional thinking is that 30 L/min is a well controlled inhalation flow rate. And, currently no data has been presented which shows that using existing metered dose inhaler technology, significant uniform and peripheral particle deposition had occurred, at any flow rate.

Finally, it is now generally believed that for a protein to be efficiently delivered systemically through the lungs, a very small particle size is required to facilitate peripheral deposition, preferably in the alveoli. The size often considered necessary for this purpose is in the range of one micron.

Statement of the Invention

Utilizing the dry powder inhalation system described in PCT/US93/09751, published 28 April 1994, and incorporated by reference (referred to here as the SPIROS

system), the following in vitro and in vivo observations have been made:

1. The in vitro delivery of several drug/lactose blends has been shown to be flow rate independent over a
5 range flow rates from 15 to 60 L/min. Both the size of the active particles and the amount of drug delivered were independent of flow rate.

2. Utilizing a radiolabelled technique, the flow rate independence of the delivery system was confirmed in
10 vivo (15 to 60 L/min). In addition, this study clearly indicated that even with a slow inhalation rate (less than 60 L/min), the drug was delivered uniformly throughout the lung, including the periphery. In fact, there is a tendency to have higher peripheral lung deposition at the
15 low flow rate.

3. In the metered dose inhaler studies, where the in vitro determined MMAD is between 2 to 3 microns, in vivo deposition is typically quoted as between 10 to 20% of the nominal dose. Deposition of albuterol from the
20 Spiros system was shown to be equal to or better than what is expected from metered dose inhalers, even though the aerodynamic particle size of the active particle was approximately 4.5 microns.

4. Recent pharmacokinetic (blood level) data from
25 a comparison of beclomethasone delivered from a metered dose inhaler compared to Spiros, indicated that twice as much drug was delivered to the lung from the Spiros system. Again, the particle size of the active particle in the dry powder inhaler system was between 4 to 5
30 microns, while the metered dose inhaler formulation was between 3 to 4 microns.

5. Using calcitonin as a model peptide for systemic delivery, the bioactivity following dosing with the Spiros system has been estimated to be greater than 20% compared to a subcutaneous injection. In contrast, an approved
5 nasal product has only 3% bioavailability. Surprisingly, the particle size of the calcitonin from the calcitonin/lactose blend was 4-5 microns, yet excellent systemic availability was achieved (>20%).

Using the above observations, the following
10 conclusions regarding dry powder delivery can now be made.

Until a dry powder inhaler was developed which adequately deaggregated the powder at low inspiratory flow rates, it was not possible to separate out the performance of the dry powder inhaler from the patient inhalation
15 maneuver. Thus, the relationship between particle size and deposition was confused with the performance of the dry powder inhaler itself. With the development of the Spiros system, we have now demonstrated that under low flow rate conditions, particle sizes which would be
20 considered on the upper end of achieving good lung deposition can actually provide deposition uniformly throughout the respiratory tract.

Importantly, the delivery of the dry powder from the Spiros system is no longer degraded by the patient's
25 inhalation flow rate, as is the case with existing dry powder inhalers. Slow deep inspiration is key to the increased drug delivery and peripheral deposition. Thus, the delivery system must efficiently operate under these conditions. With the deagglomerating dry powder at low
30 inhalation flow, surprising good results were obtained

over what could be expected for commercially available metered dose inhalers or dry powder inhalers.

The results which were obtained in vivo were possible because 1) Spiros is inhalation flow rate independent, and
5 2) Spiros efficiently deaggregates the powder. Therefore, patients were able to be trained and benefit from the slow deep inhalation maneuver. The slow deep inhalation permits more of the particles to navigate past the throat (and not be collected by impaction) and be available to
10 deposit in the lung. Secondly, the slow deep inhalation maneuver fully dilates the lungs, driving the particles further into the lung, and inhibits premature impaction of the larger particles in the upper airways.

To facilitate the slow inhalation, some device
15 resistance is required. If no resistance is encountered, then it is difficult for a patient to inhale slowly. This is what is often observed for metered dose inhalers and some dry powder inhalers such as Rotohaler and Spinhaler. If flow resistance is too high, patient discomfort results
20 when the inhaler is used at the optional flow rate. It can also result in higher air velocity in passageways. This increase in velocity increases upper airway deposition by impaction. Less deposited drug is then available to the lower regions of the lung. The drug may
25 be a systemic or topical drug for treating asthma. The drug may be a protein, a polypeptide or a hormone, for treating lung or other conditions.

Detailed Description

1. A dry powder inhalation system consisting of micronized drug in the 1 to 7 micron range, alone or in blends of lactose or some other suitable inert carrier (i.e., sugars, salts).

2. The inhalation system should be flow rate independent over the range of interest, i.e., 10 or 15 - 60 L/min.

3. The mass median aerodynamic diameter (MMAD) of the delivered aerosol (Cascade impactor 26.3 L/min, UPS throat) should be 3.5 - 7 and preferably 3 - 6 microns. Additionally, the respirable fraction (fraction of particles penetrating the impactor inlet with a particle size less than 5.8 microns) should be greater than 20%. The most preferred level would be greater than 30 to 40%. This describes the efficiency of the device to deagglomerate the powder. A device such as the Beclomethasone Rotohaler which could be considered flow rate independent over this range delivers an aerosol of 10 microns and a respirable fraction of 2.6%.

The device resistance (slope of the flow vs. pressure drop curve (in units of $\text{cm H}_2\text{O}^{1/2}$)) should be .12 to .21 with a most preferred range of 0.12 to 0.18.

Claims:

1. A method for inhalation of a dry powder drug, comprising the steps of:

- 5 a) providing a dry powder drug composition having a drug particle size of from about 1-7 microns and mass median aerodynamic diameter of the delivered aerosol of from about 3 to 6 microns;
- 10 b) loading the dry powder drug composition into an inhaler which is generally flow rate independent, and with the inhaler having an inspiration flow resistance of about .12 to .21 (cm H₂O)* over the range of about 10-60 L/min;
- 15 c) inhaling the drug composition from the inhaler with an inspiration flow rate of about 15-60 L/min, resulting in a delivery efficiency measured by respirable fraction of at least 20%.

20 2. The method of claim 1 wherein the drug composition includes active particles and the aerodynamic particle size of the active particles is about 4.5 microns.

25 3. The method of claim 1 wherein the drug comprises a systemic or a topical drug for treating asthma.

4. The method of claim 1 wherein the drug comprises a protein, a polypeptide, or a hormone.

5. The method of claim 1 wherein the percent of particles greater than 5 microns is about 30-90.

6. The method of claim 1 wherein the inhaler has a flow resistance of from about .12 to .18 (cm H₂O)*.

5 7. The method of claim 1 wherein the drug composition includes an inert carrier.

8. The method of claim 1 wherein the drug comprises beclamethasone.

10 9. The method of claim 1 wherein the respirable fraction (fraction of particles penetrating the inpactor inlet with a particle size less than about 5.8 microns) is at least 20%.

10. The method of claim 1 wherein the flow resistance is about .12 to .21 (cmH₂O)* over the range of
15 15-60 L/min.

11. The method of claim 1 wherein the mass median aerodynamic diameter of the delivered aerosol is from about 3.5 to 5.5 microns.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/06621

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/12

US CL : 424/45; 128/203.12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/45; 128/203.12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,681,752 A (MELILLO) 21 July 1987, see entire document.	1-11
Y	US 4,810,488 A (JINKS) 07 March 1989, see entire document.	1-11
Y, P	US 5,524,613 A (HABER et al.) 11 June 1996, see entire document.	1-11

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

•	Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
• A	document defining the general state of the art which is not considered to be of particular relevance		
• E	earlier document published on or after the international filing date	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
• L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
• O	document referring to an oral disclosure, use, exhibition or other means		
• P	document published prior to the international filing date but later than the priority date claimed	Z	document member of the same patent family

Date of the actual completion of the international search

20 JUNE 1997

Date of mailing of the international search report

09 JUL 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Raj Bawa, Ph.D.

Telephone No. (703) 308-2351